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European biotechnology patent case law update

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Webinar agenda

- T 0099/19 – dosage regimens - data requirements for inventive step
- T 1111/14 – essential steps
- Akebia Therapeutics Inc v Fibrogen, Inc [2020] EWHC 866 (Pat) – doctrine of equivalents
- T 2214/14 – patient subgroups – different clinical outcomes
- T 0870/14 – vaccines – comparison with prior art

T 0099/19

Dosage regimens - data requirements for inventive step

Dosage regimens

- In G 2/08 the Enlarged Board held that Article 54(5) EPC does not prevent a medicament which is already used in the treatment of an illness being patented for use in a different treatment by therapy of the same illness.
- Established in G 2/08 that a new dosage regime of a known medicament for treatment of the same illness can be novel.
- The new dosage regimen must be distinguished from the known regimen for example by the timings or effective dose used.
- The new dosage regime must also meet the requirements of inventive step.

Dosage regimens – inventive step

- Often considered to lack inventive step – the optimisation of the dose of a known drug is considered to be routine optimisation for the skilled person as the efficacy of the drug has already been shown.
- In T 1409/06, the claim read:
- “1. The use of granisetron in the manufacture of a medicament for the treatment of post-operative nausea and vomiting (PONV) wherein granisetron is administered in a 1 mg to 3 mg unit dose.”
- The Board concluded that "**mere determination of the dosage which yields the best effect does not involve an inventive step. The skilled person is aware that the intensity of a pharmacological effect depends inter alia on the concentration of the active ingredient. This is, therefore, a matter of mere routine optimization.**“
- Dosage regime patents also face the risk of the closest prior art disclosing future potential research or hypotheses.

Patenting dosage regimens

- Providing data to support a new technical effect of the claimed dosage regimen assists with inventive step assessment.
- Combining different types of dosage regimes increases the chance of the closest prior art being "more distant".
  - E.g. new dose with a new mode of administration or new dose with a new medical indication.
- Is there a prejudice in the art against the dosage?
- Effect of improving patient compliance.
  - Data is not necessarily required to evidence improved patient compliance itself.
  - E.g. claims directed to a single dose regimen, reduced dosage interval etc.

T 0099/19 – background

- Appeal from a decision of the Opposition Division to revoke the patent for added matter and insufficiency.
- Claim 1*: "**Tetrahydrobiopterin (BH4),** or optionally a salt form thereof, **for use in the treatment of a subject with phenylketonuria (PKU**), wherein the **BH4 is to be administered orally once daily at a daily dose of 5 mg/kg to 30 mg/kg**, and wherein the BH4 is to be administered in combination with a protein restricted diet."*
- PKU is caused by a deficiency in the liver enzyme phenylalanine hydroxylase (PAH).
- In non-PKU subjects, phenylalanine (Phe) is converted to tyrosine in the liver by PAH with BH4 as cofactor, keeping plasma Phe concentrations low.

T 0099/19 – decision: inventive step

- The Board of Appeal first assessed inventive step with consent of the patentee, and ultimately did not consider sufficiency of disclosure.
- The closest prior art, D21, was considered to disclose the oral use of 12 to 15 mg BH4/kg/day divided in three doses for the treatment of PKU.
- The difference between the invention and D21 is that BH4 was administered once daily to the PKU patient.

T 0099/19 – Decision: inventive step

- Board considered that the experimental data on file:
  - Credibly show that the claimed dosage regimen of BH4 provides a level of efficacy sufficient to bring about the claimed therapeutic effect.
  - Do not support that this dosage regimen maintains the same level of efficacy as the BH4 dosage regimen of the closest prior art (D21).
- Technical problem: the provision of a dosage regimen of BH4 in the treatment of PKU that leads to improved patient compliance.

T 0099/19 – decision: inventive step

- Board considered the skilled person would have applied such a dosage regimen to BH4 in an obvious manner. It was a commonly known general principle that once-daily administration of a drug provides for improved patient compliance.
- Patentee argued that a prejudice existed in the art against once-daily oral dosing of BH4 in the treatment of PKU:
  - *because of its short half-life in humans after oral administration, BH4 had to be administered to PKU patients in more than one dose per day to ensure a sufficient concentration of BH4 in the plasma.*

  Supported prejudice with expert declaration and referring to three prior art documents.

T 0099/19 – decision: inventive step

- According to the case law of the boards of appeal, a prejudice in any particular field relates to an opinion or preconceived **idea widely or universally held by experts in that field**. The existence of such prejudice is normally demonstrated by reference to the literature or encyclopaedias published before the priority date.
- The prejudice must have existed at the priority date; any prejudice which might have developed later is of no concern in the judgement of inventive step (Case Law of the Boards of Appeal", 9th edition 2019, I.D.10.2).

T 0099/19 – decision: inventive step

Board considered the alleged prejudice not to be conclusively proven.

- No indication that the skilled person would have concluded that oral once-daily dosing of BH4 would not be sufficient to treat PAH deficiencies from the cited documents.

- The skilled person would have expected once-daily administration of BH4 to result in a lesser decrease of serum Phe concentrations than BH4 administered at two doses per day. However, no indication which would have led the skilled person to conclude that oral once-daily dosing of BH4 would not be sufficient to treat PAH deficiencies

T 0099/19 – lessons

- If claiming reduced dosage to improve patient compliance, consider including data showing at least similar efficacy is achieved as compared with the known use.
- Lack of such data directly comparing the invention with the prior art can lead to the formulation of a less ambitious objective technical problem.
- When the objective technical problem concerns improved patient compliance, it would be beneficial to substantiate that a prejudice existed in the art against the claimed dosage regimen/mode of administration.
- Need very convincing evidence to prove a technical prejudice.

T 1111/14
Oregon Health & Science University
In vitro methods – essential steps

T 1111/14 – background

- Appeal from a decision of the Examining Division to refuse the application under Article 84, Article 83 EPC and exceptions to patentability (Article 53(a) EPC).
- Claim 1: "*A method of expanding human hepatocytes in vivo, comprising: (i) transplanting isolated human hepatocytes into a Rag2-/- IL2rg-/- mouse, wherein the mouse is deficient for expression of Fah; (ii) allowing the human hepatocytes to expand for at least about two weeks; and (iii) collecting human hepatocytes from the mouse.*"
- The focus of the arguments both before the ED and the Board of Appeal was on whether the additional step of administering a vector encoding human urokinase (uPA) to the mouse at issue was an essential step.

Essential step – Article 84 EPC

- It is a requirement for patentability under **Article 84 EPC** that the claims define clearly all the essential features of the invention.
- Essential features are those necessary for achieving a technical effect underlying the solution of the objective technical problem.
- Any features which do not actually contribute to the solution of the problem are not essential features, even if these features are consistently mentioned throughout the description of the invention.

T 1111/14 – ED decision

- The ED acknowledged that the urokinase (uPA) vector pre-treatment is not mentioned as essential.
- However, ED maintained that it is not unambiguously derivable that it is possible to achieve the desired technical effect (expanding human hepatocytes into FRG mice) without uPA.
- ED took a narrow view that the disclosure of embodiment without uPA treatment was only as more than a 'try and see‘ possibility".
- ED also considered the failure rate in the Examples to cast doubt on the invention working in the absence of uPA treatment.

T 1111/14 – decision under Article 84 EPC

- The Board of Appeal held that uPA treatment is not an essential step.

- "*The quoted passages disclose, clearly and unambiguously, an embodiment of the invention that does not require the administration of a uPA vector to the mouse prior to transplantation.* ***The amount of technical details provided in the application for this particular embodiment might have to be considered for the assessment of sufficiency of disclosure, but it is of no relevance as regards the question whether claim 1 is supported by the description. Otherwise, the boundary between the requirements of Articles 83 and 84 EPC becomes blurred.***"

T 1111/14 – decision under Article 83 EPC

- Example in application states:
- "*In three separate transplantations, primary engraftment of human hepatocytes was observed in FRG mice in recipients which had first received the uPA adenovirus.* ***The uPA-pretreatment regimen was therefore used in most subsequent transplantation experiments****.*
- *In total, human hepatocytes from nine different donors were used successfully* ***and no engraftment failures occurred after introduction of the uPA adenovirus regimen****.*" (see page 43, lines 13 to 18 of the application; emphasis as in the decision under appeal).

T 1111/14 – decision under Article 83 EPC

- Board held that the claimed invention is sufficiently disclosed.
- Board cited that "some engraftment failures" cannot be equated to a failure to carry out the claimed method without administration of uPA.
  - "*Occasional failure when testing a technical teaching does not impair its reproducibility, if the attempts are kept within reasonable bounds and do not require inventive skill.*"
- Board considered that in the technical field at issue occasional failure is the rule, rather than the exception.

T 1111/14 – lessons

- Confirms the distinction between the requirements of Articles 83 and 84 EPC.
- No requirement to expressly state in the description that a feature of the invention is not essential to achieve the technical effect.
- A low success rate can still be used to support that an invention is enabled as long as the invention can be reproduced without inventive skill – especially if low success rates are normal in the field of the invention.

[2020] EWHC 866 (Pat)
Akebia Therapeutics Inc v Fibrogen, Inc
Doctrine of equivalents – interplay between validity and infringement

Doctrine of equivalents

- Broadens the effective scope of a patent claim – allows patentees to seek remedies for infringement of a patent claim by a product or process falling outside the literal meaning of a claim.
- A patentee could argue in favour of the validity of a narrow claim during examination and then seek to claim infringement of a broader, and potentially invalid claim, under the doctrine of equivalents post-grant.
- Until now there has been little clarification from the courts on whether this apparent abuse of procedure would be sanctioned.

Doctrine of equivalents – Actavis UK Ltd and others v Eli Lilly and Company

Actavis questions:

i. Notwithstanding that it is not within the literal meaning of the relevant claim(s) of the patent, does the variant achieve substantially the same result in substantially the same way as the invention, i.e. the inventive concept revealed by the patent?

ii. Would it be obvious to the person skilled in the art, reading the patent at the priority date, but knowing that the variant achieves substantially the same result as the invention, that it does so in substantially the same way as the invention?

iii. Would such a reader of the patent have concluded that the patentee nonetheless intended that strict compliance with the literal meaning of the relevant claim(s) of the patent was an essential requirement of the invention?

(For infringement need to answer “yes”, “yes”, “no”.)

Akebia v Fibrogen – background

- Akebia Therapeutics, and Otsuka Pharmaceutical challenged the validity of six patents belonging to FibroGen to clear the way for launch of their **vadadustat** product for the **treatment of anaemia associated with chronic kidney disease (CKD)**.
- The patents related to inhibitors of the enzyme hypoxia inducible factor-prolyl hydroxylase (HIF-PHIs) for use in treating anaemia and related disorders.
- During the validity action, FibroGen had limited a number of claims to one specific chemical compound (compound C) for reasons of sufficiency.
- FibroGen then argued that claims limited to compound C were infringed by vadadustat under the doctrine of equivalents.

Akebia v Fibrogen – questions (i) & (ii)

- The High Court held that the first two questions should be answered “no”.
  - does the variant achieve substantially the same result in substantially the same way as the invention, i.e. the inventive concept revealed by the patent? = no.
  - Would it be obvious to the person skilled in the art, reading the patent at the priority date, but knowing that the variant achieves substantially the same result as the invention, that it does so in substantially the same way as the invention? = no.
- Primarily due to structural differences between compound C and vadadustat.
- This means that the claims are not infringed under the doctrine of equivalents.
- In spite of this conclusion, the court considered the third question.

Akebia v Fibrogen – question (iii)

- Would such a reader of the patent have concluded that the patentee nonetheless intended that strict compliance with the literal meaning of the relevant claim(s) of the patent was an essential requirement of the invention? = yes.
- The High Court confirmed that limiting a claim to a specific compound for reasons of validity must be interpreted as "*disclaiming the other ways of achieving the same effect disclosed in the specification, and in particular everything covered by the broader granted claims.*"
- The High Court also confirmed that any generic statements made during prosecution to suggest that deleted subject-matter has not been abandoned or that the claims have been limited merely to expedite prosecution should not affect this conclusion.

Akebia v Fibrogen – implications

- The reasoning presented in the decision deviates from the conclusion reached in Actavis UK Ltd and others v Eli Lilly and Company in that:
  - It suggests that the reader of a patent would be aware of limitations required to achieve a valid claim.
  - It concludes that the reader would consider limitations made to achieve validity to require strict compliance with the literal meaning of the claim (leading to a finding of non-infringement).
- Could be distinguished from Actavis UK Ltd v Eli Lilly by the type of amendment required - added matter is a formal ground but sufficiency is a fundamental requirement for patentability.

Akebia v Fibrogen – lessons

A patentee may not be permitted **under certain circumstances** to make a limiting amendment for reasons of validity but then argue in favour of a broader claim when assessing infringement.

- Whether an amendment is likely to be taken to require strict compliance with the wording of the claims should be considered with caution.
- The reason for an amendment and the similarity of the potential infringement to subject-matter excluded from the claim by the amendment both appear to be important factors for consideration.

T2214/14
Baxter International Inc
Patient subgroups

Patient subgroups

- Established at the EPO that the use of a known compound to treat a known disease in a new group of patients can be novel.
- The new patient subgroup must be distinguished from the former by its *physiological or pathological status* (T19/86).
- Choice of patient subgroup cannot be arbitrary, such that there is no functional relationship between the physiological or pathological status of the new patient subgroup and the therapeutic or pharmacological effect achieved (T1399/04).
- Novelty requirements for patient subgroups akin to low level inventive step.

T2214/14 – background

- Appeal from a decision of the Examining Division to refuse an application for insufficiency and lack of inventive step.
- Claim 1*: "A composition for use in reversing Type-1 diabetes in a mammal having new onset diabetes, the composition comprising microspheres comprising oligonucleotides that are antisense to and targeted to bind to primary transcripts selected from the group consisting of CD40, CD80 and CD86 primary transcripts, and combinations thereof."*
- Amended claims filed in appeal proceedings dealt with sufficiency issue.
- Examining Division had found claim 1 to lack an inventive step over D2.

T2214/14 – ED inventive step decision

- Application as filed included evidence that the claimed microspheres reversed disease in diabetic mice.
- D2 described a microsphere composition comprising the oligonucleotides of claim 1.
- Example 4 of D2 demonstrated that mice treated with the microspheres took longer to develop diabetes than untreated mice, but no data using mice with diabetes was included.
- The Examining Division considered claim 1 to lack inventive step because the skilled person would have been able to predict that the claimed microspheres would resolve diabetes.

T2214/14 – decision: inventive step

- Board of Appeal found all claims to be inventive.
- D2 was considered to demonstrate only that the claimed microspheres could prevent the development of diabetes in non-diabetic NOD mice.
- The difference between the invention and D2 is the reversal of diabetes v the prevention of diabetes.
- The technical problem was the provision of a composition comprising the antisense molecules for achieving a **further, different clinical outcome**.

T2214/14 – decision: inventive step

- D4 was a review article considered to form part of the common general knowledge.
  - 175 agents shown to delay or prevent onset of type 1 diabetes.
  - only 6 of these agents shown to reverse diabetes once it developed.
  - Many agents shown to be efficacious in pre-diabetic animals have proven to be ineffective in new onset diabetic mice.
- Hope that a treatment may be successful is not enough for a reasonable expectation of success.

T2214/14 – lessons

- Disease prevention and disease treatment are considered different clinical outcomes.
  - Reduces the relevance of prior art relating to the same disorder unless evidence of treatment provided.
  - Confirms importance of CGK regarding uncertainty of therapy.
- Appeal process conducted in writing – possibility of avoiding Oral Proceedings advantageous in present circumstances.

T0870/14
GlaxoSmithKline Biologicals SA
Vaccines - comparison with prior art

Meningitis vaccines – GSK & Novartis

- Both GSK & Novartis had large vaccine portfolios, both protecting their own innovation and covering the other's innovation.
- In 2015 GSK acquired Novartis' vaccine business (excluding influenza) and divested its oncology business.
- Many patents acquired by GSK had previously been the subject of GSK oppositions.
- Meningitis vaccines formed a large part of both portfolios.

T0870/14 – background

- Opposed patent relates to a combination of a conjugated MenW135 capsular saccharide antigen and a conjugated Hib capsular saccharide antigen.
- Claim 1: "*An aqueous immunogenic composition which, after administration to a subject, is able to induce an immune response that is (a) bactericidal against at least serogroup W135 of N.meningitidis and (b) protective against H.influenzae type b disease,*

  wherein the composition comprises:

  (i) a conjugated serogroup W135 capsular saccharide antigen; and

  (ii) a conjugated H.influenzae type b ('Hib') capsular saccharide antigen;

  & wherein the serogroup W135 saccharide is conjugated to a diphtheria toxoid."

T0870/14 – OD decision

- OD found claim 1 to lack an inventive step over D7 in view of D13.
- D7 discloses the combination of unconjugated W135 & conjugated Hib.
- Difference relative to D7 is conjugation of W135 saccharide antigen.
- Claims considered to be obvious in view of D13 which discloses MenACWY conjugated to diphtheria toxin.
- Claim 6 found to add matter:
  - No basis for combination of the diphtheria toxin being CRM197 and less than 30µg meningococcal saccharide.

T0870/14 – decision: closest prior art

- GSK provided arguments in favour of D6 or D13 as the CPA.
- D6 discloses MenACW135Y conjugated to diphtheria toxin.
- D13 discloses MenACW135Y conjugated to diphtheria toxin.
- D7 discloses combination of unconjugated MenW135 & conjugated Hib.
- Board concluded that D7 is the CPA.
- "*Whether other documents constitute a more promising starting point is immaterial … since the Board holds that the claimed invention is obvious when starting from … D7*".

T0870/14 – decision: inventive step

- The difference between D7 and the opposed patent is the presence of meningococcal saccharides in conjugated form.
- The Opposition Division considered the effect of the difference to be improved immunogenicity of the meningococcal saccharides.
- The Opposed Patent compared MenACWY conjugate compositions in the presence and absence of a Hib conjugate.
- The Opposed Patent did not compare conjugated and unconjugated saccharides and no effect is demonstrated in the patent.
- The Board considered that the effect of this difference (improved immunogenicity of the saccharides) was plausible from the common general knowledge.

T0870/14 – decision: inventive step

- The Board concluded that the objective technical problem is the provision of a composition for immunisation against infection by *N. meningitides* and *H.influenza* with improved immunogenicity.
- D13 discloses MenACW135Y conjugated to diphtheria toxin.
- The Board concluded that the skilled person would have modified the vaccine of D7 using the conjugate of D13.
- This modification would have achieved improved immunogenicity, as taught in D13.

T0870/14 – lessons

- If you do not have data directly comparing the invention with the prior art then common general knowledge can be used to determine the technical effect of a difference.
  - This can lead to the formulation of a more ambitious problem.
  - If the technical effect is demonstrated by the prior art (including CGK) the claims are obvious.
- This situation can be avoided by providing data comparing the invention with the closest prior art.
  - In the application as filed or as post-filed data.
- Changing closest prior art may not be effective to achieve inventive step.
- Opposition withdrawn after appeal has been filed will still be considered by the Board of Appeal.

Thank you for listening

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